

/application-reviews/AP1-08047

AP1-08047: Accelerated development of a combined gene and stem cell therapy to treat amyotrophic lateral sclerosis (ALS)

SCORES AND RECOMMENDATIONS

Score: <65

GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)

Therapeutic candidate: This project will use a powerful combined neural progenitor cell and growth factor approach to treat patients with amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease). Human neural progenitor cells can be isolated and expanded in culture to large banks of billions of cells. When transplanted into animal models of ALS they have been shown to mature into support cells for dying motor neurons called astrocytes. In other studies, growth factors such as glial cell line-derived growth factor (or GDNF) have been shown to protect motor neurons from damage in a number of different animal models including ALS. However, delivering GDNF to the spinal cord has been almost impossible as it does not cross from the blood to the tissue of the spinal cord. By directly transplanting the modified stem cells in the spinal cord, they will be located in the vicinity of sick motor neurons. A number of advances in stem cell biology along with new surgical devices have allowed us to develop this approach for the treatment of ALS.

The disease: There are approximately 5,600 new cases of ALS in the USA each year and as many as 30,000 Americans may currently be affected by ALS. The initial features of the disease include muscle twitching, cramping, stiffness, muscle weakness affecting an arm or a leg, slurred and nasal speech, and difficulty chewing or swallowing. This quickly progresses to full paralysis. Most patients are likely to die of respiratory failure, ALS amenable to cell/gene therapy approaches as it is an incurable and terminal disease, with a very high cost/risk benefit ratio.

Rationale for proposed therapy: (i) astrocytes surrounding dying motor neurons are also affected by ALS, and thus lose their nurturing capacity for the sick motor neurons and (ii) powerful growth factors such as glial cell line-derived neurotrophic factor (GDNF) can protect motor neurons in animal models.

Our new accelerated development award: The focus of this new proposal will be to perform essential preclinical studies in both small and large animals that will establish optimal doses and safe procedures for continuing the administration of cells to other segments of the cord. Expanding on the clinical data to be gained in our original award where cells will be transplanted into one side of the lumbar spinal cord (that supplies the legs with neural impulses), we propose to in parallel advance the development to a second clinical study delivering the cells to the cervical region of the spinal cord where potential impact on breathing can be measured. The additional information gained by this second study will allow for us to determine if, in addition to establishing that this approach is safe in both regions of the spinal cord, to determine whether a higher dose or more injection can lead to greater clinical effect, and whether a series of functional measures are predictive of slowing progression of this devastating disease.

Statement of Benefit to California (provided by applicant)

ALS is a devastating disease, and also puts a large burden on state resources through the need of full time caregivers and hospital equipment. It is estimated that the cost of caring for an ALS patient in the late stage of disease while on a respirator is \$200,000-300,000 per year. While primarily a humanitarian effort to avoid suffering, this project will also ease the cost of caring for ALS patients in California if ultimately successful. As the first trial in the world to combine stem cell and gene transfer of a growth factor, California will also take the lead as a center of excellence for these types of therapeutic strategies. This in turn will attract scientists, clinicians, and industry interested in this area of medicine to the state of California, thus increasing state revenue and state prestige in the rapidly growing field of Regenerative Medicine.

REVIEW SUMMARY

This application focuses on the development of a genetically modified neural progenitor cell therapy for amyotrophic lateral sclerosis (ALS). ALS is a degenerative motor neuron disease characterized by muscle wasting for which there is currently no cure and only

modestly effective treatment. Under the CIRM-funded Parent Award, the applicant is performing activities required to support the filing of an Investigational New Drug (IND) application with the FDA. The Parent Award also supports a Phase 1 clinical trial of unilateral transplantation of the therapeutic candidate into the lumbar spinal cord of patients with ALS. Activities proposed in the current application can be grouped into three areas: 1) manufacturing optimization and scale-up; 2) additional preclinical animal studies to support cell transplantation into the cervical spinal cord; and 3) a second Phase 1 clinical trial of bilateral lumbar and cervical transplantation to be run in parallel to the trial funded by the Parent Award.

Clinical Competitiveness and Impact of the Proposed Therapy

- There are competing cell therapy programs for ALS that are further along in clinical development but none have demonstrated efficacy. The applicant's approach is unique in its combination of cell and gene therapies.

Strength of the Development Program

- Reviewers described the development plan as superficial. It is not clear what outcomes of the Phase 1 trial would compel a Phase 2. The favored efficacy endpoint and desired margin of improvement are not specified.

- The argument for moving from unilateral lumbar injections to bilateral and then cervical is strong. Cervical injections may offer the best chance to impact quality of life and survival.

Qualifications of Development Team

- The team is very strong scientifically, both in the areas of neural stem cell biology and ALS.

- A reviewer recommended using the NEALS consortium as a source of ALS natural history data and to inform aspects of clinical trial design and statistical powering.

Progress on Parent Award and Effective Program Leadership

- The Parent Award has suffered some setbacks and delays related to manufacturing. Reviewers described these as critical issues that need to be addressed and resolved before accelerating activities should be considered. They noted that these issues could further impact the timeline of the Parent Award and delay proposed activities.

- Reviewers agreed that the team is generally making good progress under the Parent Award, despite some significant setbacks.

Relevance of the Therapeutic to Regenerative Medicine

- The therapeutic candidate is clearly relevant to regenerative medicine.

Proposed Activities for Acceleration of the Development Program

- Reviewers agreed that the proposed manufacturing optimization and scale-up activities are worthwhile but that their request for additional funding is premature given the status of manufacturing under the Parent Award.

- Reviewers supported the goal of testing bilateral and cervical injections in a clinical trial but questioned the proposed plan and timeline. Some reviewers suggested waiting for clinical data from the unilateral lumbar trial before designing the next clinical study. Other reviewers felt that the development program, as a whole, could be accelerated by delaying the timeline of the Parent Award and doing preclinical studies with cervical injections. These studies could support both lumbar and cervical injections in the same Phase 1 clinical trial.

- Reviewers would have appreciated a more detailed response to the most recent FDA letter. They noted several FDA comments that could affect the design of preclinical studies.

Feasibility of Proposed Activities for Acceleration of the Development Program

- Reviewers were concerned about the feasibility of the proposed preclinical timeline, given manufacturing delays and the need to lock down the design of the delivery device.

- Reviewers also questioned the feasibility of the clinical timeline, specifically whether the FDA would allow bilateral and cervical injections prior to the availability of safety data from unilateral lumbar injections.

Conflicts:

Nazem Atassi

Adrian Gee

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